ARRHYTHMIAS AND ELECTROLYTE DISTURBANCES*

BORYS SURAWICZ

Cardiovascular Division, Department of Medicine
The University of Kentucky College of Medicine, Lexington, Ky.

NEW information derived from the electrophysiological laboratory, in particular from studies employing microelectrodes, has contributed to a more rational approach to the diagnosis and treatment of cardiac arrhythmia. The purpose of this paper is to correlate some of the recent advances in electrophysiology of cardiac fibers with the effect of electrolytes on cardiac rhythm and conduction in man. For a review of cellular electrophysiology the reader is referred to textbooks,[1, 2] review articles,[3, 4] and to the article of B. F. Hoffman in this symposium. This presentation will be divided into three parts: potassium and arrhythmia; other electrolytes and arrhythmia; and effect of electrolytes on the action of digitalis and antiarrhythmic drugs.

POTASSIUM AND ARRHYTHMIA

Hyperpotassemia. Increased extracellular K concentration may alter rhythm and conduction by one or more of the following mechanisms: 1) decreased resting or maximal diastolic membrane potential; 2) increased velocity of repolarization and shortening of the action potential (AP); 3) decreased rate of diastolic depolarization, and increased threshold potential in the pacemaker fibers. Arrhythmias may be also caused by: 4) differences in sensitivity to K among different types of cardiac fibers,[5,6] and 5) "injury currents" resulting from differences in potassium concentration in different parts of the myocardium. The negative inotropic effect of potassium may also possibly play an indirect role in the production of arrhythmia.

Electrocardiographic pattern of hyperpotassemia. When plasma K concentration exceeds approximately 5.5 mEq./l., the T waves become tall and peaked, and the Q-T interval shortens. Further increase of plasma K concentration results in decrease of the amplitude of the P

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wave, and progressive widening of both the P wave and the QRS complex. P waves disappear when plasma K concentration exceeds about 8.8 mEq./l. Hyperpotassemia usually increases the duration of the QRS complex uniformly; this suggests diffuse slowing of conduction without change in the sequence of depolarization. The peaking of the T wave and the shortening of the Q-T interval are related to the increased velocity of phase 3 and shortening of the ventricular action potential. The progressive slowing of the intra-atrial and intraventricular conduction is attributed to a slower rate of rise of the AP caused by the less negative resting membrane potential.[7] The P wave disappears when the ventricular complex is still well defined because the atrial fibers become nonexcitable at lower K concentrations than the ventricular fibers.[8] When the P wave disappears and the rhythm remains regular, the pacemaker may be displaced from the S-A mode into the A-V node, the bundle of His, or into the Purkinje fibers. However, even in the absence of atrial depolarization, the impulse from the S-A node may propagate to the ventricles, presumably through specialized atrial fibers.[9] This may result in sinoventricular conduction in the presence of sino-atrial block. When plasma K concentration exceeds about 10 mEq./l., the ventricular rhythm may be irregular, and multiple escape pacemakers may appear in the depressed myocardium. The combination of an irregular rhythm and an absent P wave may simulate atrial fibrillation. An increase of plasma K concentration above 10-14 mEq./l. causes ventricular asystole or ventricular fibrillation. In isolated preparations the bundle of His is most "resistant" to increased extracellular K concentration. An action potential from the bundle was recorded when all other cardiac fibers were nonexcitable.[10] Ventricular fibrillation is probably due to reentry, which is facilitated by the slow intraventricular conduction and the short duration of the ventricular AP.

Administration of potassium salts. The effect of K administration on cardiac rhythm and conduction depends on the integrity of the myocardium, the initial plasma K concentration, the amount of administered K, and the change or the rate of change of plasma K concentration. Administration of potassium may produce the following effects: 1) suppression of supraventricular and ventricular ectopic beats and rhythms; 2) shortening or lengthening of the A-V conduction time; 3) atrial and ventricular standstill; 4) defibrillation of the atria and

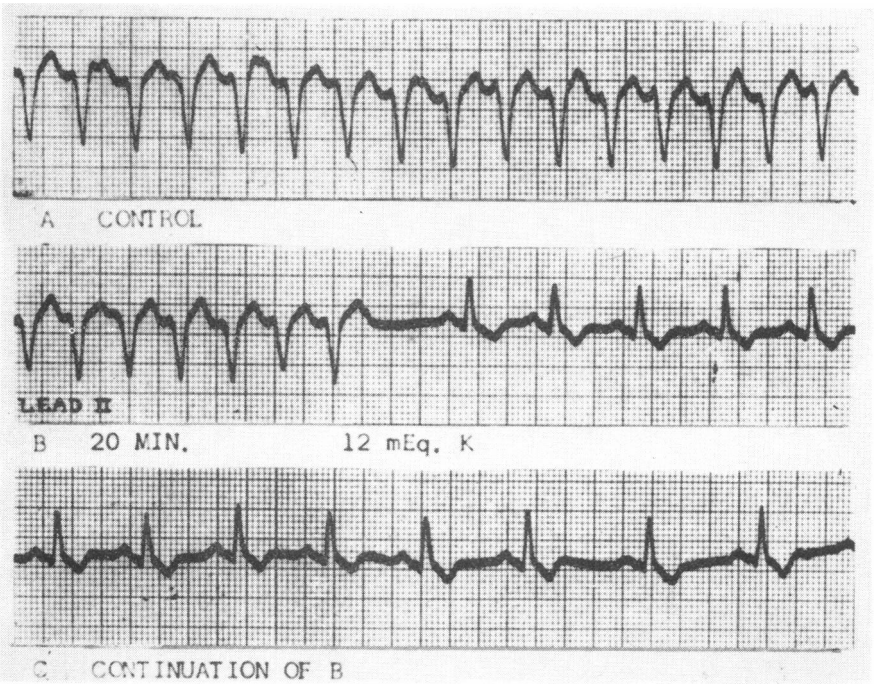

Fig. 1. Abrupt termination of ventricular tachycardia during intravenous KCl administration. (From B. Surawicz, in: *Cardiovascular Drug Therapy*, p. 467. Brest, A. N. and Moyer, J. H., eds, New York, Grune, Stratton, 1965. Courtesy of publishers).

the ventricles; 5) ventricular fibrillation; 6) increase of ectopic beats.

Intravenous administration of K at a rate of 0.5-1.0 mEq./min. suppresses supraventricular and ventricular ectopic beats and rhythms with the exception of atrial fibrillation and atrial flutter in about 80 per cent of patients.[11] The antiarrhythmic effect usually occurs when plasma K concentration is increased by 0.5-1.0 mEq./l. to a level of 5.0-6.5 mEq./l. Such increase of plasma K concentration usually has no effect on the sinus rate. The disappearance of ectopic beats is probably due to slowing of diastolic depolarization and increase of the threshold potential of the ectopic pacemaker fibers. Administration of K may occasionally terminate an ectopic supraventricular or ventricular tachycardia abruptly (Figure 1). More commonly, however, the rate of the ectopic rhythms decreases gradually (Figure 2). Increased K concentration slows diastolic depolarization in Purkinje fibers more than in the fibers of the S-A node.[12] This may explain the suppression of ectopic activity without change of the sinus rate. Slowing of the rate of diastolic de-

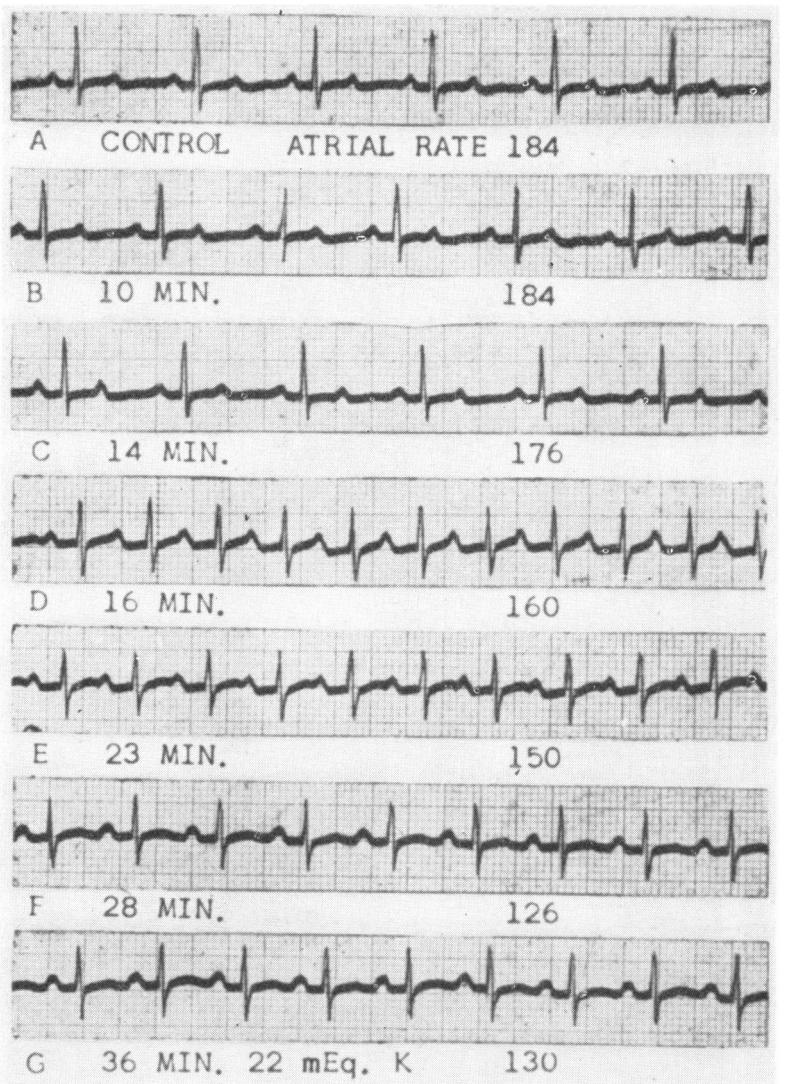

Fig. 2. Gradual decrease of atrial rate during intravenous KCl administration in a patient with ectopic atrial tachycardia. In the strips *A, B,* and *C,* 2:1 A-V conduction; in D-G, 1:1 conduction. (From B. Surawicz, in: *Cardiovascular Drug Therapy,* p. 463. Brest, A. N. and Moyer, J. H., eds., New York, Grune, Stratton, 1965. Courtesy of publishers).

polization in the Purkinje fibers by potassium is attributed to increased potassium permeability.[13-14]

The effect of moderate increase of plasma K concentration on the A-V conduction in man is variable. In some patients, increase of plasma K concentration to 5.0 to 6.5 mEq./l. shortens the P-R interval and

abolishes second or third degree A-V block.[11] In other patients the same increase of plasma K concentration may have either no effect or a depressing effect on A-V conduction.[11] The net effect of hyperpotassemia on A-V conduction is determined by the complex interrelation between the change of the resting membrane potential, threshold potential, and the slope of diastolic depolarization in the fibers of the conducting system.[15] The less negative resting membrane potential and threshold potential may result in slower conduction. However, the decreased rate of diastolic depolarization may cause more rapid conduction in fibers depolarized from a more negative diastolic potential. Slight depolarization may also increase A-V conduction velocity by bringing the maximal diastolic potential closer to the threshold potential. In addition, shortening of the AP may also possibly contribute to more rapid conduction. Clinical observations suggest that the most rapid A-V conduction in man probably occurs at K concentrations that are somewhat above the upper limits of normal K concentration. The individual variations may depend on pathological factors such as the degree of damage of the conducting system in the diseased heart, and also on physiological variables such as the complex interplay between potassium and acetylcholine.[16, 17] When plasma K concentration exceeds 8.0 mEq./l. the P-R interval is usually prolonged. When this occurs, the P amplitude is low, and it may be difficult to determine whether the prolongation of the P-R interval is due to the increased duration of the P wave or the duration of the P-R segment.

Cardiac arrest occurs when K depolarizes ventricular fibers to a critical level at which the fibers become nonexcitable.[17] Another type of cardiac arrest has been observed in isolated perfused hearts after a change from K-deficient solution to one containing normal K concentrations.[18] In the rabbit heart this type of arrest was attributed to inhibition of diastolic depolarization of the pacemaker fibers, presumably due to sudden increase of K conductance.[18] The resting membrane potential of the atrial and ventricular fibers was not appreciably decreased at the time of inhibition of the pacemaker, and there were no intraventricular or intra-atrial conduction disturbances before or after arrest.[18] The same phenomenon was also observed in K-depleted dogs.[19] Bradycardia and A-V conduction disturbances that occasionally occur in patients with hypopotassemia during rapid administration of K salts may be caused by the same mechanism (references 83 and 84 in Surawicz [15]).

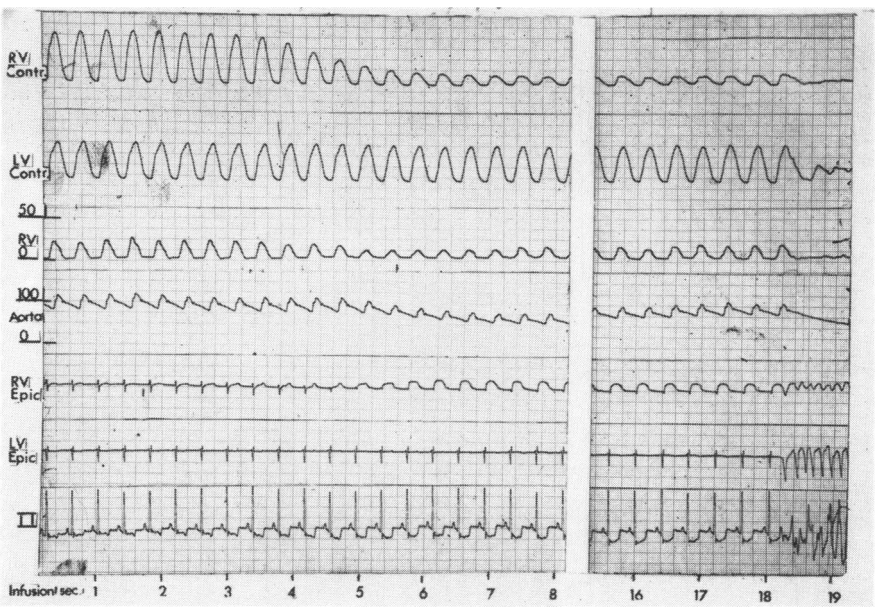

Fig. 3. Infusion of 6.5 ml. of isotonic KCl solution containing 0.26 mEq. of K into right coronary artery of 20 kg. dog within 15 seconds. Note: Onset of ventricular fibrillation after single ventricular ectopic beat 3 seconds after the end of infusion. There is no change in heart rate, and no increase of QRS duration before the premature beat. See text. Abbreviations: R. V. Contr. and L. V. Contr. = right and left ventricular contractile force measured with strain gauge arches sutured to the surface of the ventricles; R.V. = right ventricular pressure in mm. Hg; Aorta = aortic pressure in mm. Hg; R.V. Epic. and L.V. Epic. = right and left ventricular epicardial electrograms; II = Lead II. (Unpublished observations of A. Krotkiewski and B. Surawicz).

The above observations suggest that rapid rates of change of plasma K concentration may depress the formation and conduction of impulses. The effect of K administration on intraventricular conduction may also depend on the rate of change of plasma K concentration. For instance, slow administration of K in dogs produces a gradual increase of the QRS interval, but rapid administration produces first a decrease and then an increase in the duration of the QRS complex.[19]

In dogs, administration of potassium salts intravenously at a rapid rate produces either ventricular standstill or ventricular fibrillation. The latter occurs more frequently than the former. Ventricular fibrillation usually develops when plasma K concentration in the coronary arteries exceeds 15 to 20 mEq./l. Fibrillation may be either preceded by several ventricular ectopic beats with wide QRS complexes, or it may occur after a single premature beat without preceding change of heart

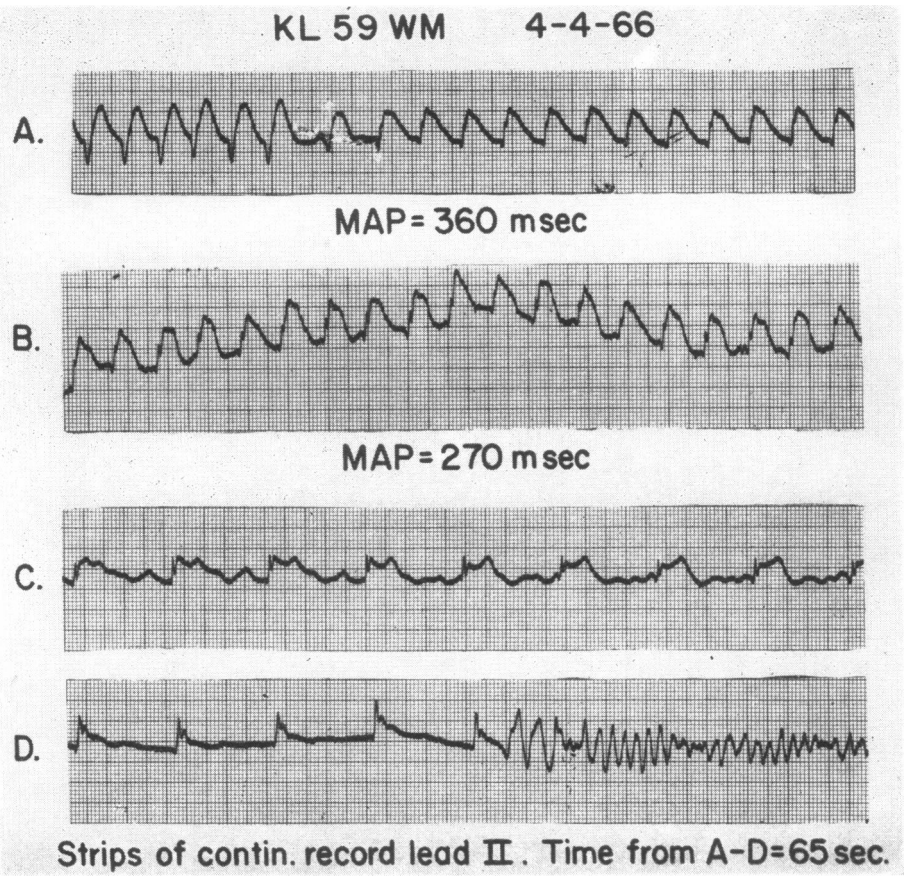

Fig. 4. Electrocardiogram of a 59-year-old man with acute myocardial infarction. Note: Monophasic pattern in *A* and *B*, elevation of the S-T segment in *C* and *D*, and onset of ventricular fibrillation after single ventricular premature beat in *B*. Duration of ventricular depolarization + repolarization (MAP) is 360 msec. in *A*, and 270 msec. in *B*. Coupling interval of the premature beat = 300 msec.

rate or increase of QRS duration.[15] Figure 3 demonstrates ventricular fibrillation that occurred after administration of 0.26mEq. K into the right coronary artery of a dog in 15 seconds. In the electrogram from the area perfused by potassium the Q-T interval is shortened and the S-T segment is elevated, while the ventricular complex is unchanged in the electrogram from the area not perfused by potassium. Ventricular fibrillation occurs after a single ventricular premature beat. The appearance of this premature beat after administration of K is difficult to explain because hyperpotassemia should decrease the automaticity of pacemaker fibers. Patients with hyperpotassemia usually have

no ectopic beats before the onset of severe intraventricular conduction disturbances. It is conceivable that the ectopic beat is caused by the "current of injury" resulting from the nonhomogeneous distribution of potassium.

It is of interest that ventricular fibrillation in patients with acute myocardial infarction (Figure 4) closely resembles fibrillation produced by administration of potassium into the coronary arteries (Figure 3). Common to both are "injury current," shortening of ventricular repolarization, absence of QRS widening and increase of heart rate, as well as short coupling interval of the premature beat. The short coupling interval implies a short effective refractory period, and suggests that premature depolarization occurs in the area in which plasma K concentration is increased. Ectopic rhythms after coronary occlusion in dogs have been attributed to potassium liberated from the infarcted myocardium.[20] Since moderate hyperpotassemia lowers the threshold of excitability, an increase of K concentration could render some pacemaker fibers susceptible to excitation by the injury current.[21]

The defibrillatory effect of K has been known since 1908.[22] Atria can be defibrillated by lesser increase of plasma K concentration than the ventricles. In patients with severe hyperpotassemia, spontaneous change from atrial fibrillation to sinus or an ectopic atrial rhythm may take place at K concentrations about 8 to 9 mEq./l. The literature contains several reports of atrial defibrillation after administration of potassium salts (references 54 and 62 in Surawicz[15]).

In certain potassium-depleted patients with severe hypopotassemia, ectopic activity increased during the administration of potassium with glucose.[23] These arrhythmias may be due to the decreased potassium concentration that frequently occurs during slow administration of potassium with glucose. It is probable that glucose metabolism contributes to the migration of potassium into the cells and lowers plasma K concentration.[23]

Potassium and artificial pacemakers. In dogs the ventricular threshold of excitability decreases when plasma K concentration is moderately elevated[24, 25] but increases sharply when K concentration exceeds about 7 to 9 mEq./l.[24-26] Systematic studies of excitability threshold in man have not been carried out. Several clinical observations suggest that slight increases of plasma potassium concentration lower the threshold of ventricular excitability while further increases raise the threshold. An

example of the lowering of excitability threshold by potassium is its effect on the function of defective pacemakers in which either the stimulus strength is decreased or the tissue resistance around the electrode is increased. Occasionally normal response to pacemaker stimulation can be restored by the administration of potassium salts.[27] Administration of glucose and insulin that lowers plasma K concentration may cause a decreased responsiveness to the stimulation by defective pacemakers. We observed a marked increase of the ventricular excitability threshold in a patient with a transvenous pacemaker when his plasma K concentration was increased to 7.1 mEq./l.[26] The measurement of excitability threshold in patients with pacemakers does not differentiate between a lack of response to stimulation and the lack of propagation of a local response. However, this is probably of little practical significance since both excitability threshold and conduction velocity are probably affected in the same manner. The lowest excitability threshold and the most rapid conduction velocity in man may occur when plasma K concentration is close to 6.0 mEq./l. while lower and higher K concentrations are expected to decrease the conduction velocity and increase the excitability threshold. There may be differences between the extracellular K concentrations that depress intraventricular conduction disturbances *in vivo* and *in vitro*. In the isolated papillary muscle and Purkinje fibers of the monkey, velocity of conduction increased when extracellular K was 8.1 mM./l., and decreased when K concentration was 10.8 mM./l.[28] In dog and in man P-R and QRS intervals are usually prolonged when plasma K concentration exceeds 7.0 mEq./l.

Hypopotassemia. Decreased extracellular K concentration may alter rhythm and conduction by one or more of the following mechanisms: 1) increased resting membrane potential (hyperpolarization); 2) shortening of phase 2 and prolongation of phase 3 of AP; 3) increased rate of diastolic depolarization in the pacemaker fibers; 4) transformation of nonpacemaker into pacemaker fibers; 5) decrease of excitability threshold. Arrhythmias may be also caused by differences in the response of different fiber types to the same decrease of plasma K concentration. The effects of low K on the electrophysiological properties of the S-A node, A-V node, and the bundle of His have been studied less extensively than the effects of high K on these structures. Therefore the mechanisms of some electrocardiographic manifestations of

hypopotassemia still remain uncertain. Moderate hypopotassemia alters mainly repolarization but severe hypopotassemia may also cause intraventricular and A-V conduction disturbances. The depression of the S-T segment, decreased amplitude of the T-wave, and increased amplitude of the U wave are attributed to shortening of phase 2 and prolongation of phase 3 of the ventricular AP.[29] The AP becomes longer but this apparently does not increase the duration of the effective refractory period, because most of the AP increase occurs at the end of repolarization when the fiber has repolarized to a level that is below the threshold potential. When the AP develops a long and slow "tail," the membrane potential may be actually closer to the threshold potential that would facilitate depolarization. In isolated preparations depression of potassium concentration may change nonpacemaker fibers into pacemaker fibers.[15] The effect of hypopotassemia on the atrial and ventricular refractory period has not been studied. Clinical observations suggest that hypopotassemia shortens the effective refractory period because atrial and ventricular premature beats in patients with hypopotassemia frequently occur after a short coupling interval.[30] Perfusion of isolated rabbit hearts with potassium-deficient solutions produces intraventricular conduction disturbances and A-V block as well as supraventricular and ventricular ectopic beats.[7, 29] In patients with severe hypopotassemia, the QRS interval is usually increased by 0.01 to 0.03 seconds.[31] The increased duration of the QRS complex is the result of widening without change in shape, which suggests that it is caused by slower intraventricular conduction without change in the sequence of depolarization. This may be due to hyperpolarization of ventricular fibers, or to slower conduction in the specialized fibers of the conducting system. Hypopotassemia prolongs the "tail" of the action potential in the conducting systems more than in the ventricles, so that the period of incomplete repolarization in the Purkinje fibers is longer than in the ventricular fibers.[32] In addition, hypopotassemia increases the velocity of diastolic depolarization in the Purkinje fibers.[13, 32] Therefore, quiescent Purkinje fibers develop automatic activity. When such fibers are depolarized from a level of transmembrane potential that is less negative than the maximal diastolic potential, the upstroke velocity of the AP and the conduction velocity decrease. Depolarization of incompletely repolarized ventricular fibers may also produce intraventricular conduction disturbance (Figure 5). Patients

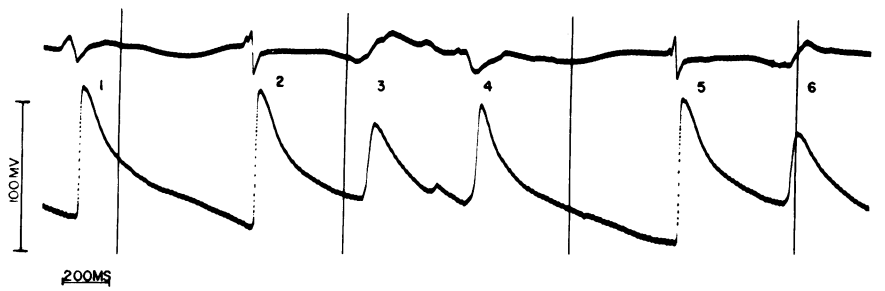

Fig. 5. Ventricular ectopic beats and ECG during perfusion of an isolated rabbit heart with Krebs-Hanseleit solution containing 0.8 mm. K and 12 mg. quinidine per liter. When depolarization begins from a more negative membrane potential (1st, 2d, and 5th beats), the upstroke of the action potential (AP) is more rapid than when depolarization begins from a less negative membrane potential (3d, 4th, and 6th beats). In beats with slower upstroke, the QRS complexes are wider and less well defined than in beats with more rapid upstroke. (L. S. Gettes, B. Surawicz, and J. C. Shiue, *Amer. J. Physiol. 203*:1135, 1965. Courtesy of publishers).

with severe hypopotassemia may occasionally have advanced disturbances of intraventricular conduction.[33] Hypopotassemia promotes the appearance of supraventricular and ventricular ectopic beats and rhythms. In 81 nondigitalized patients with plasma K concentration 3.2 mEq./l. or less, ventricular ectopic beats occurred in 28 per cent, supraventricular ectopic beats in 22 per cent, and A-V conduction disturbances in 12 per cent.[30] Ectopic beats occurred three times, and A-V conduction disturbances two times more frequently than in the control hospital population.[30] The prevalence of ectopic beats in patients with hypopotassemia who had no digitalis and no heart disease was at least twice as great as in the control group of unselected hospital patients.[30] It is of interest that patients with severe hypopotassemia may develop arrhythmias that are considered characteristic of digitalis toxicity, e.g., nonparoxysmal atrial tachycardia with block, or A-V dissociation. Arrhythmias of this type are attributed to a combination of increased automaticity of ectopic pacemakers, and at least some degree of atrioventricular conduction disturbances. The mechanism of depressed A-V conduction caused by low potassium has not been studied at the cellular level. It is probable that the effect of low potassium on the pacemaker fibers in the A-V junction is similar to the effect of low K on the Purkinje fibers. Patients with hypopotassemia have greater sensitivity to vagal stimulation.[34] It should be added that in some patients A-V conduction may be improved by decreasing plasma K concentration. This is probably the basis of therapy with chlorothiazide in

patients with incomplete A-V block.[35]

Perfusion of isolated hearts with potassium-deficient solutions produces ventricular fibrillation.[29, 36] This may be due to a combination of increased ventricular automaticity, slowing of conduction, and short effective refractory period. Ventricular fibrillation has also occurred in patients with severe hypopotassemia.[23]

Other Ions in Arrhythmia

Calcium. Only extremely high or low concentrations of Ca produce electrophysiologic abnormalities that are of clinical importance. Within the range of concentrations compatible with life, calcium has relatively little effect on the resting membrane potential. Low calcium prolongs and high calcium shortens phase 2 of the AP in several types of cardiac fibers.[37] Calcium does not alter appreciably the duration of phase 3. Prolongation of phase 2 by low calcium prolongs the duration of the AP and the duration of the effective refractory period. Shortening of phase 2 by high calcium shortens the duration of the AP and the duration of the effective refractory period. The same change of Ca concentration may have different effects on the phase 2 of different types of cardiac fibers.[37] The effect of calcium on the duration of the AP depends on heart rate and magnesium concentration.[37, 38] It is of interest that low calcium does not prolong the duration of the action potential in premature beats when the depolarization begins from a significantly less negative membrane potential than the resting potential.[39] Low calcium depresses contraction, lowers excitability threshold, and slightly decreases the rate of diastolic depolarization of the pacemaker fibers.[40] High calcium increases the contractile force, increases excitability threshold, and slightly increases the rate of diastolic depolarization of the pacemaker fibers.[40]

Experimental hypercalcemia increases the duration of the QRS complex and produces ectopic beats and ventricular fibrillation.[15] Patients with severe hypercalcemia may have prolonged QRS and P-R intervals and, occasionally, second- or third-degree A-V block.[41] The incidence of ectopic beats in patients with hypercalcemia does not appear to be increased. It has been postulated that sudden deaths of patients with hyperparathyroidism and other disturbances producing hypercalcemia are caused by ventricular fibrillation.[14] However, there are no published electrocardiograms of patients with hypercalcemia

shortly before or at the time of sudden death.

Perfusion of isolated hearts with calcium-deficient solutions produced ectopic beats and ventricular fibrillation only when calcium concentration was less than 1/20 of the normal plasma calcium concentration.[42] Patients with hypocalcemia are not expected to have conduction disturbances or ectopic beats. Hypocalcemia induced by administration of Na_2EDTA suppressed supraventricular and ventricular ectopic beats in about 50 per cent of patients.[43] Ectopic beats suppressed by hypocalcemia reappeared after calcium administration.[43] We have suggested that the antiarrhythmic effect of induced hypocalcemia may be due to the prolonged duration of the effective refractory period.

The effect of calcium on the electrophysiologic properties of the heart depends on potassium concentration. In isolated hearts, intraventricular conduction disturbance, A-V conduction disturbances, and ventricular fibrillation caused by increased extracellular potassium concentration can be abolished or prevented by increasing calcium concentration. Conversely, intraventricular conduction disturbances, atrioventricular conduction disturbances, and ventricular fibrillation caused by low extracellular K concentration can be abolished or prevented by lowering calcium concentration. Administration of calcium shortens the QRS duration when K concentration is increased, probably because high calcium concentration maintains normal resting membrane potential in the presence of increased K concentration.[37]

The mechanism by which low levels of calcium prevent conduction disturbances and fibrillation in hearts perfused with solutions low in K is not clear. Low calcium does not alter the amount or the rate of K loss in the heart.[44] The clinical significance of the observations that low calcium inhibits arrhythmias produced by low potassium is uncertain. The antiarrhythmic effect of low calcium in hearts perfused with low potassium solution occurred when calcium concentrations were much lower than those encountered in patients with hypocalcemia. Patients with combined hypopotassemia and hypocalcemia had the same prevalence of ectopic beats as patients with hypopotassemia without hypocalcemia.[30]

Sodium. High sodium concentration increases and low sodium concentration decreases the upstroke velocity of the action potential. Within limits of plasma sodium concentration compatible with life, the effect of high or low sodium on cardiac rhythm and conduction are probably

negligible. However, in patients with intraventricular conduction disturbances caused by hyperpotassemia, hypernatremia shortens and hyponatremia prolongs the QRS interval. Intravenous administration of sodium salts effectively suppresses manifestations of advanced K cardiotoxicity and prevents ventricular standstill and fibrillation (references 30-32 in Surawicz[15]).

Magnesium. High extracellular concentrations of magnesium depress atrioventricular and intraventricular conduction. The depression of A-V conduction may occur when magnesium concentration is 3 to 5 mM./l. and cardiac arrest may be expected when magnesium concentration reaches 15 to 22 mM./l. (references 17 and 31 in Surawicz *et al.*[38]) The latter concentrations are considerably higher than those that cause respiratory arrest. Intravenous administration of magnesium salts suppresses ectopic beats in both digitalized and nondigitalized patients.[45] The effect of high magnesium on the upstroke velocity of the ventricular action potential is similar to the effect of high potassium. The mechanism of the antiarrhythmic action of magnesium therefore may be similar to that of potassium. In the isolated preparation high magnesium decreases and low magnesium increases the duration of the atrial and ventricular action potential when Ca concentration is low.[38] This suggests that abnormal magnesium concentration may alter the duration of the effective refractory period in patients with hypocalcemia (Ref. in 38).

Effect of Electrolytes on the Action of Digitalis and Antiarrhythmic Drugs

Digitalis. Increased extracellular potassium concentration decreases automaticity and suppresses ectopic beats induced by digitalis.[46-51] Hyperpotassemic animals and man can tolerate unusually large doses of digitalis without developing ectopic activity.[52, 53] In hypopotassemic animals ectopic beats and rhythms appear after administration of unusually small doses of glycosides.[53] In patients receiving digitalis, arrhythmia may be precipitated by carbohydrate administration or removal of potassium by dialysis.[54-56] The effects of the interaction of potassium and digitalis on A-V conduction reflect the complex effects of potassium on A-V conduction. As mentioned earlier, both extremes, low and high potassium concentration, depress A-V conduction. Therefore, moderate hyperpotassemia may improve A-V conduction in patients with A-V block induced by digitalis.[11] However, in dogs and in

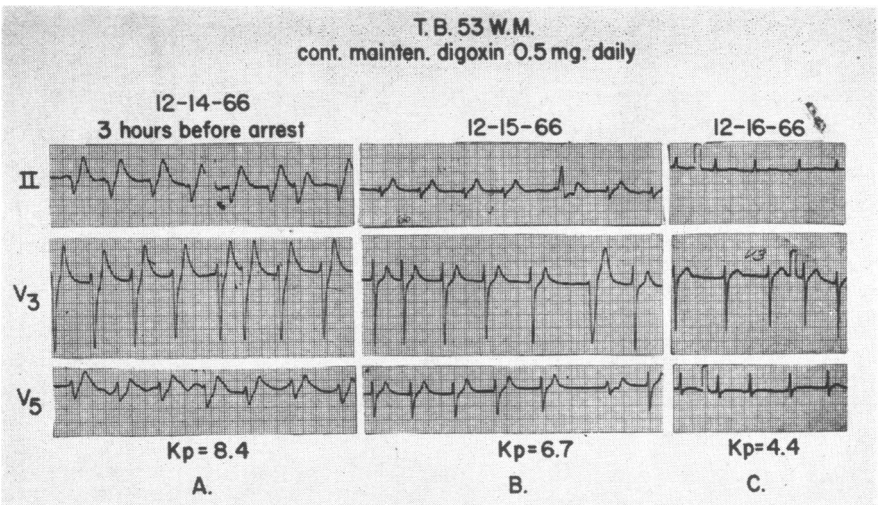

Fig. 6. Electrocardiogram of a 53-year-old patient with atrial fibrillation, treated with a maintenance dose of 0.5 mg. digoxin daily. Note: Pattern of hypopotassemia three hours before "cardiac arrest" (*A*), and after treatment with sodium lactate, glucose and insulin (*B* and *C*). Ventricular rate in *A*, *B*, and *C* is about 95/minute. The sixth beat in *B* is probably a ventricular escape beat.

man, hyperpotassemia and digitalis may also have a synergistic depressive effect on A-V conduction.[57, 58] The effects of hyperpotassemia on A-V conduction disturbance induced by digitalis are not predictable because they depend not only on the absolute plasma K concentration but on the rate of K administration and on the presence or absence of structural damage of the conducting system. Figure 6 demonstrates an ECG of a patient with atrial fibrillation and renal insufficiency treated with a maintenance dose of 0.5 mg. digoxin daily. In this patient the rhythm and the rate are the same when plasma K concentration is 8.4 (*A*), 6.7 (*B*), 4.4 (*C*) mEq./l. In other patients with atrial fibrillation receiving digitalis, hyperpotassemia produced complete A-V block with an A-V junctional pacemaker. The rate of the A-V junctional pacemaker was normal or rapid.* It is possible that in dogs with digitalis-induced disturbances of A-V conduction, depression of A-V conduction may be due to a rapid rate of K administration rather than to hyperpotassemia. At present there is not enough clinical evidence to suggest that administration of potassium is contraindicated in patients with depression of A-V conduction produced by digitalis. It remains to be established whether patients receiving digitalis develop arrest or fibrillation at lower K concentrations than patients without

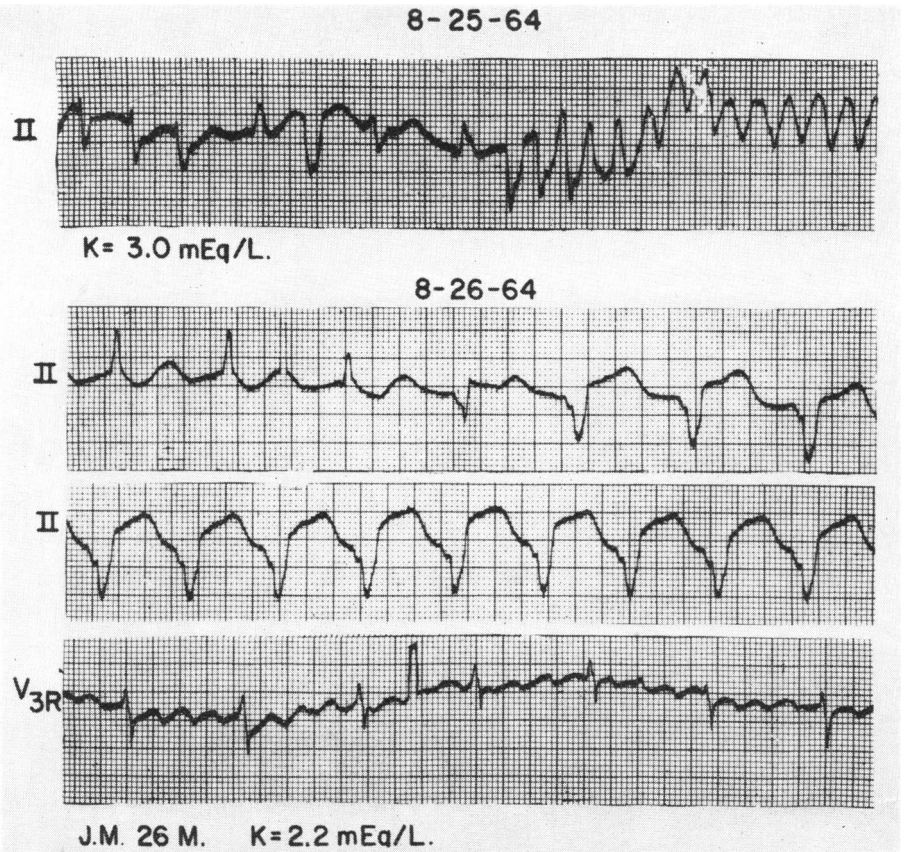

Fig. 7. Electrocardiogram of a 26-year-old patient with rheumatic heart disease, treated with a maintenance dose of 0.25 mg. digoxin daily. On August 25, 1964, atrial fibrillation with multiple ventricular ectopic beats. Ventricular fibrillation begins after premature beat with a short coupling interval. On the following day, ECG pattern of hypopotassemia, and atrial fibrillation with regular ventricular rhythm attributed to a complete A-V block. Note: Transition from A-V junctional rhythm to a ventricular ectopic escape rhythm in lead II. (From: S. Davidson and B. Surawicz, Ectopic beats and atrioventricular conduction disturbances in patients with hypopotassemia. In press. Courtesy of *Arch. Int. Med.*)

digitalis. The effect of potassium appears to depend more on the rate of K administration and the presence or absence of structural damage of the conducting system than on the absolute plasma K concentration.

Hypopotassemia may augment the depression of A-V conduction produced by digitalis. The most characteristic arrhythmias in hypopotassemic patients receiving digitalis are nonparoxysmal supraventricular tachycardia with block and dissociation. Both types of arrhythmia

*Surawicz and Gettes, unpublished observations.

are due to a combination of increased ectopic activity and depressed A-V conduction. Both hypopotassemia and digitalis decrease the effective refractory period of the ventricles and shorten the coupling interval of ventricular premature beats. Slow propagation of early ectopic impulses may result in reentry and cause ventricular fibrillation (Figure 7). The synergistic effect of low K and digitalis on automaticity and A-V conduction explains the increased sensitivity to digitalis in patients with hypopotassemia. We have seen the appearance of nonparoxysmal atrial tachycardia with block or A-V dissociation with A-V junctional tachycardia after the administration of 0.75-2.0 mg. of digoxin in patients with hypopotassemia and K-depletion.*

There is a lack of detailed studies of the calcium-digitalis relationship on the electrophysiological properties of cardiac fibers.[59] Both hypercalcemia and digitalis increase the threshold of excitability and shorten the effective refractory period in the ventricles. It has been reported that hypercalcemia increases the susceptibility of the heart to the induction of ventricular ectopic beats by ouabain.[60, 61] Several studies suggest a synergistic effect of calcium and digitalis on automaticity (references in Surawicz[62]). But in experimental animals receiving digitalis, hypercalcemia produced ectopic rhythms only when the animals had received an excess of 95 per cent of the toxic dose of ouabain. Dogs that received 90 per cent of the toxic dose of acetylstrophanthidin had no arrhythmia when their serum calcium was 46.2 mg. per cent. In another study, nondigitalized dogs developed A-V block when serum calcium concentration was 15 to 40 mg. per cent. Ectopic rhythms terminating in ventricular fibrillation were associated with slightly higher calcium concentrations.[64] The effects of calcium on animals receiving digitalis were not different from those in animals not receiving digitalis, so that this study showed no evidence of synergistic or additive effects between calcium and digitalis. Clinical correlations between the effects of hypercalcemia and digitalis are surprisingly scarce; hence the problem requires further investigation. Ectopic beats caused by overdosage of digitalis are suppressed by lowering calcium concentration with Na_2 EDTA or citrate salts.[62] However, it has been pointed out that Na_2EDTA is equally effective in suppressing ectopic beats and rhythms in digitalized and nondigitalized patients.[43]

Quinidine. In animal experiments the effect of hyperpotassemia

*Surawicz and Mortelmans, unpublished observations.

and quinidine on the rate of rise of the AP and the conduction velocity are synergistic. Therefore quinidine toxicity is augmented by hyperpotassemia.[65] The effect of low K concentration is less predictable. The hyperpolarizing effect could counteract the quinidine effect on conduction. Such an effect was observed in isolated rabbit hearts beating at a slow rate.[66] However, in dogs or in isolated rabbit hearts beating at a more rapid rate the intraventricular conduction disturbance produced by quinidine became more pronounced when K concentration was low.[7, 67] In isolated hearts this was attributed to a greater prolongation of repolarization by low K and quinidine together than by either alone. Thus the onset of depolarization usually occurred before the repolarization was completed. This resulted in a slower rate of rise of the action potential and a slow conduction (Figure 5). Toxic effects of quinidine on atrioventricular and intraventricular conduction in dogs can be reversed by the administration of sodium chloride or sodium lactate.[67, 68] This is apparently caused by increased rate of rise of the action potential mediated by sodium. Administration of calcium increases the duration of the P-R and QRS intervals in dogs with quinidine intoxication.[68] However, this effect of calcium is not greater in quinidine-intoxicated dogs than in control animals. When quinidine-intoxicated dogs developed sinus bradycardia, increased potassium concentration further slowed the heart rate. However, decreased plasma K concentration and increased sodium or calcium concentration had no effect on the sinus rate.* The effects of electrolytes on the A-V and intraventricular conduction produced by quinidine are similar to those in dogs not receiving quinidine. The only exception is shortening of the PR and QRS intervals by sodium in dogs with quinidine intoxication. However, this effect of sodium is not specific since it is also present when conduction is depressed by potassium and other factors.

Summary

This article reviews: 1) correlation of recent advances in electrophysiology of cardiac fibers with the effects of electrolytes on rhythm and conduction in man; 2) arrhythmias due to electrolyte disturbances and the effect of certain electrolyte disturbances on preexisting arrhythmias; 3) treatment of arrhythmias by altering plasma electrolyte concentrations; and 4) effects of electrolyte disturbances on the action of digitalis and quinidine.

*Mazzoleni and Surawicz, unpublished observations.

REFERENCES

1. Hoffman, B. F. and Cranefield, P. F. *Electrophysiology of the Heart.* New York, McGraw-Hill, 1960.
2. Weidmann, S. *Elektrophysiologie der Herzmuskelfaser.* Bern, Huber, 1956.
3. Trautwein, W. Generation and conduction of impulses in the heart as affected by drugs, *Pharmacol. Rev. 15:*277, 1963.
4. Woodbury, J. W. Cellular Electrophysiology of the Heart. In: *Handbook of Physiology.* Circulation, vol. I, Chap. 2, p. 237.
5. deMello, W. C. and Hoffman, B. F. Potassium ions and electrical activity of specialized cardiac fibers, *Amer. J. Physiol. 199:*1125, 1960.
6. Paes de Carvalho, A. and Langan, W. B. Influence of extracellular potassium levels on atrioventricular transmission, *Amer. J. Physiol. 205:*375, 1963.
7. Gettes, L. S., Surawicz, B. and Shiue, J. C. Effect of high K, and low K, and quinidine on QRS duration and ventricular action potential, *Amer. J. Physiol. 203:*1135, 1962.
8. Lepeschkin, E., Surawicz, B., and Herrlich, H. C. Differences in the effect of electrolytes on the atrial and ventricular action potentials of isolated perfused rabbit hearts, *Fed. Proc. 19:*112, 1960.
9. Vassalle, M. and Hoffman, B. F. The spread of sinus activation during potassium administration, *Circ. Res. 17:*285, 1965.
10. Vassalle, M., Greenspan, K., Jomain, S. and Hoffman, B. F. Effects of potassium on automaticity and conduction of canine hearts. *Amer. J. Physiol. 207:* 334, 1964.
11. Bettinger, J. C., Surawicz, B., Bryfogle, J. W., Anderson, B. N. and Bellet, S. The effect of intravenous administration of potassium chloride on ectopic rhythms, ectopic beats and disturbances in A-V conduction, *Amer. J. Med. 21:*521, 1956.
12. Antoni, H., Herkel, K. and Fleckenstein, A. Die Restitution der automatischen Erregungsbidung in Kaliumgelähmten Schrittmacher-Geweben durch Adrenalin, *Pflueger Archiv. Ges. Physiol. 277:*633, 1963.
13. Vassalle, M. Cardiac pacemaker potentials at different extra- and intracellular K concentrations, *Amer. J. Physiol. 208:*770, 1965.
14. Vassalle, M. Analysis of cardiac pacemaker potential using a "voltage clamp" technique, *Amer. J. Physiol. 210:*1335, 1966.
15. Surawicz, B. Role of electrolytes in etiology and management of cardiac arrhythmias, *Progr. Cardiov. Dis. 8:* 364, 1966.
16. Feigenbaum, H., Wunsch, C. and Fisch, C. Effect of intracoronary infusion of potassium on the vagal action on A-V transmission, *J. Clin. Invest. 44:*399, 1965.
17. Greenspan, K., Wunsch, C. and Fisch, C. The relationship between potassium and vagal action, on atrioventricular transmission, *Circ. Res. 17:*39, 1965.
18. Surawicz, B. and Gettes, L. S. Two mechanisms of cardiac arrest produced by potassium, *Circ. Res. 12:*415, 1963.
19. Surawicz, B., Chlebus, H. and Mazzoleni, A. Hemodynamic and electrocardiographic effects of hyperpotassemia. Differences in response to slow and rapid increases in concentration of plasma K, *Amer. Heart J. 73:*647, 1967.
20. Harris, A. S., Bisteni, A., Russell, R. A., Brigham, J. C. and Firestone, J. E. Excitatory factors in ventricular tachycardia resulting from myocardial ischemia: potassium a major excitant, *Science 119:*200, 1954.
21. Harris, A. S. Potassium and experimental coronary occlusion, *Amer. Heart J. 71:*797, 1966.
22. Wiggers, C. J. Defibrillation of the ventricles (editorial). *Circ. Res. 1:*191, 1953.
23. Kunin, A. S., Surawicz, B. and Sims, E. A. H. Decrease in serum potassium concentrations and appearance of cardiac arrhythmias during infusion of potassium with glucose in potassium depleted patients, *New Eng. J. Med. 266:*228, 1962.
24. Siebens, A. A., Hoffman, B. F., Ensen, Y., Farrell, J. E. and Brooks, C. M.

Effects of l-epinephrine and l-norepinephrine on cardiac excitability, *Amer. J. Physiol. 175:*1, 1953.

25. Han, J., Garcia de Jalon, P., and Moe, G. K. Adrenergic effects on ventricular vulnerability, *Circ. Res. 14:*516, 1964.
26. Surawicz, B., Chlebus, H., Reeves, J. T. and Gettes, L. S. Increase of ventricular excitability threshold by hyperpotassemia, *J.A.M.A. 191:*1049, 1965.
27. Walker, W. J., Elkins, J. T. and Wood, L. W. Effect of potassium in restoring myocardial response to a subthreshold cardiac pacemaker, *New Eng. J. Med. 271:*597, 1964.
28. Antoni, H. and Zerweck, T. Besitzen die sympathischen Ueberträgerstoffe einen direkten Einfluss auf die Leitungsgeschwindigkeit des Säugetiermyokards? *Pflueger Arch. Ges. Physiol. 293:*310, 1967.
29. Surawicz, B., Lepeschkin, E., Herrlich, H. C. and Hoffman, B. F. Effect of potassium and calcium deficiency on the monophasic action potential, electrocardiogram and contractility of isolated rabbit hearts, *Amer. J. Physiol. 196:* 1302, 1959.
30. Davidson, S. and Surawicz, B. Ectopic beats and atrioventricular conduction disturbances in patients with hypopotassemia, *Arch. Int. Med. 120:*280, 1967.
31. Surawicz, B. Relation between electrocardiogram and electrolytes, *Amer. Heart J. 73:*814, 1967.
32. Gettes, L. and Surawicz, B. Comparison of K effects on Purkinje and ventricular action potentials of perfused moderator band, *Fed. Proc. 26:*594, 1967.
33. Cherry, J. C. and Surawicz, B. Unusual effects of potassium deficiency on the heart of a child with cystinosis, *Pediatrics 30:*414, 1962.
34. Marini, A., Cenacchi, U., Cenciotti, L. and Galliani, A. Effetto dell' acetilcolina e della stimolazione vagale sull' elettrocardiogramma in condizioni di aumentato gradiente K intracellulare/K extracellulare, *Gior. di Clin. Med. 40:* 939, 1959.
35. Tobian, L. Prevention of Stokes-Adams seizures with chlorothiazide, *New Eng. J. Med. 265:*623, 1961.
36. Grumbach, L., Howard, J. and Merrill, J. Factors related to the initiation of ventricular fibrillation in the isolated heart: Effect of calcium and potassium, *Circ. Res. 5:*452, 1954.
37. Hoffman, B. F. and Suckling, E. E. Effect of several cations on transmembrane potentials of cardiac muscle, *Amer. J. Physiol. 186:*317, 1956.
38. Surawicz, B., Lepeschkin, E. and Herrlich, H. C. Low and high magnesium concentrations at various calcium levels. Effect on the monophasic action potential, electrocardiogram, and contractility of isolated rabbit hearts, *Circ. Res. 9:*811, 1961.
39. Surawicz, B., Dulin, M. L. and Graham, M. D. Role of refractoriness and duration of vulnerable phase in precipitation of ventricular fibrillation (V.F.) by low Ca, *Fed. Proc. 23:*261, 1964.
40. Temte, J. V. and Davis, L. D. Effect of calcium concentration on the transmembrane potentials of Purkinje fibers, *Circ. Res. 20:*32, 1967.
41. Voss, D. M. and Drake, E. H. Cardiac manifestations of hyperparathyroidism, with presentation of a previously unreported arrhythmia, *Amer. Heart J. 73:*235, 1967.
42. Weiss, D. L., Surawicz, B. and Rubenstein, I. Myocardial lesions of calcium deficiency causing irreversible myocardial failure, *Amer. J. Pathol. 48:*653, 1966.
43. Surawicz, B., MacDonald, M. G., Kaljot, V. and Bettinger, J. C. Treatment of cardiac arrhythmias with salts of ethylenediaminetetraacetic acid (EDTA), *Amer. Heart J. 58:*493, 1959.
44. Gettes, L. S., Surawicz, B. and Kim, K. H. Role of myocardial K and Ca in initiation and inhibition of ventricular fibrillation, *Amer. J. Physiol. 211:*699, 1966.
45. Szekely, P. The action of magnesium on the heart, *Brit. Heart J. 8:*115, 1946-47.
46. Sampson, J. J., Albertson, E. C. and Kondo, B. The effect on man of potassium administration in relation to digitalis glycosides with special reference to

blood serum potassium, the ECG and ectopic beats, *Amer. Heart J. 26*:164, 1943.

47. Enselberg, C. D., Simmons, H. G. and Mintz, A. A. The effects of potassium upon the heart, with special reference to the possibility of treatment of toxic arrhythmias due to digitalis, *Amer. Heart J. 39*:713, 1950.
48. Lown, B. and Levine, H. D. *Atrial Arrhythmias, Digitalis and Potassium.* New York, Lansberger, 1958.
49. Vassalle, M. and Greenspan, K. Effects of potassium on ouabain induced arrhythmias, *Amer. J. Cardiol. 12*:692, 1963.
50. Von Müller, P. Kalium und Digitalistoxizität, *Cardiologia 42*:1, 1962.
51. Fisch, C., Knoebel, S. B., Feigenbaum, H. and Greenspan, K. Potassium and the monophasic action potential, ECG, conduction and arrhythmias, *Progr. Cardiov. Dis. 8*:387, 1966.
52. Williams, J. F., Klocke, F. J. and Braunwald, E. Studies on digitalis. XIII. A comparison of the effects of potassium on the inotropic and arrhythmic producing actions of ouabain, *J. Clin. Invest. 45*:346, 1966.
53. Lown, B., Weller, J. M., Wyatt, N., Hoigne, R. and Merrill, J. P. Effects of alterations of body potassium on digitalis toxicity, *J. Clin. Invest. 31*:648, 1952.
54. Page, E. Precipitation of ventricular arrhythmias due to digitalis by carbohydrate administration, *Amer. J. Med. 19*:169, 1955.
55. Lubash, G. D., Cohen, B. D., Braveman, W. S., Rubin, A. L. and Luckey, E. H. ECG changes during hemodialysis with the artificial kidney, *Circulation 19*:552, 1959.
56. Lown, B. and Levine, S. A. Current concepts in digitalis therapy, *New Eng. J. Med. 250*:771, 819, 866, 1954.
57. Fisch, C., Greenspan, K., Knoebel, S. B. and Feigenbaum, H. Effect of digitalis on conduction of the heart, *Progr. Cardiov. Dis. 6*:343, 1964.
58. Fisch, C., Martz, B. L. and Priebe, F. H. Enhancement of potassium-induced atrioventricular block by toxic doses of digitalis drugs, *J. Clin. Invest. 39*:1885, 1960.
59. Hoffman, B. F. and Singer, D. H. Effect of digitalis on activity of cardiac fibers, *Progr. Cardiov. Dis. 7*:226, 1964.
60. Bower, J. O. and Mengle, H. A. K. The additive effect of calcium and digitalis, *J.A.M.A. 106*:1151, 1936.
61. Gold, H. and Edwards, D. J. The effects of ouabain on the heart in the presence of hypercalcemia, *Amer. Heart J. 3*:45, 1927-28.
62. Surawicz, B. Use of the chelating agent, EDTA, in digitalis intoxication and cardiac arrhythmias, *Progr. Cardiov. Dis. 2*:432, 1959-60.
63. Lown, B., Black H. and Moore, F. D. Digitalis-electrolytes and the surgical patients, *Amer. J. Cardiol. 6*:309, 1960.
64. Smith, P. K., Winkler, A. W. and Hoff, H. E. Calcium and digitalis synergism: The toxicity of calcium salts injected intravenously into digitalized animals, *Arch. Intern. Med. 64*:322, 1939.
65. Bennett, L. L., Rubin, M. L., Blevins, C. E. and Baird, B. The effects of infusing quinidine sulfate and potassium chloride, separately and combined on conduction times of the dog heart, *Amer. Heart J. 61*:500, 1961.
66. Watanabe, Y., Dreifus, L. S. and Likoff, W. Electrophysiologic antagonism and synergism of potassium and antiarrhythmic agents, *Amer. J. Cardiol. 12*:702, 1963.
67. Mazzoleni, A. and Surawicz, B. Dissociation between the effect of quinidine on the electrical and mechanical properties of the heart in dog, *Fed. Proc. 22*:247, 1963.
68. Bellet, S., Hamdan, G., Samlyo, A. and Lara, R. The reversal of cardiotoxic effects of quinidine by molar lactate: An experimental study, *Amer. J. Med. Sci. 237*:165, 1959.